AMENDMENTS TO THE CLAIMS

Please amend the claims as shown in the marked-up copy to read as follows:

Claim 1 (Currently Amended): A method for producing a protein having an antithrombotic activity, which comprises replacing, in a protein that has an amino acid sequence having a homology of not less than 30% to the amino acid sequence of SEQ ID NO: 1 and forms a ~~higher order~~ secondary or tertiary structure composed of a first β strand (β1), a first a helix (αl), a second α helix (α2), a second β strand (β2), a loop, a third β strand (β3), a fourth β strand (β4) and a fifth β strand (β5) in this order from the amino terminus, at least one amino acid residue in a region from α2 to β2 ~~and/or~~ , a region from β3 to β4, or in the regions from α2 to β2 and from β3 to β4 so that electric charge of the amino acid residue is ~~changed~~ substituted towards positive direction as compared to the unsubstituted amino acid.

Claim 2 (Currently Amended): The method according to Claim 1, wherein at least one acidic amino acid residue in the region from α2 to β2 ~~and/or~~ , a region from β3 to β4, or in the regions from α2 to β2 and from β3 to β4 is replaced with a neutral amino acid residue to change electric charge of the amino acid residue towards positive direction as compared to the unsubstituted amino acid.

Claim 3 (Currently Amended): The method according to Claim 1 ~~or 2~~, wherein the protein originates from *Crotalus horridus horridus*.

Claim 4 (Currently Amended): The method according to ~~any one of Claims 1 to 3~~ Claim 1, wherein the region from α2 to β2 in the protein corresponds to the sequence of the amino acid numbers 47 to 72 in the amino acid sequence of SEQ ID NO: 1 and the region from β3 to β4 corresponds to the sequence of the amino acid numbers 94 to 111 in the amino acid sequence of SEQ ID NO: 1.

Claim 5 (Original): The method according to Claim 4, wherein at least one acidic amino acid residue of which α carbon atom exists within 10 Å from the α carbon atom of the arginine residue of the amino acid number 103 in the amino acid sequence of SEQ ID NO: 1 is replaced with a neutral amino acid residue.

Claim 6 (Original): The method according to Claim 5, wherein the acidic amino acid residue is at least one residue selected from the aspartic acid residue of the amino acid number 54, the aspartic acid residue of the amino acid number 101 and the glutamic acid residue of the amino acid number 106 in the amino acid sequence of SEQ ID NO: 1.

Claim 7 (Currently Amended): The method according to ~~any one of Claims 1 to 6~~ Claim 1, which further comprises deleting a region containing the loop structure existing between β2 and β3 in such a manner that the ~~higher order~~ secondary or tertiary structures of β2 and β3 are maintained, or replacing the region with one or more amino acid residue(s) in a number required to maintain the ~~higher order~~ secondary or tertiary structures of β2 and β3, said amino acid residue(s) being selected from the group consisting of a glycine residue, an alanine residue, a serine residue and a cysteine residue.

Claim 8 (Original): The method according to Claim 7, wherein the region containing the loop structure existing between β2 and β3 is replaced with an amino acid sequence composed of four glycine residues.

Claim 9 (Currently Amended): The method according to ~~any one of Claims 1 to 8~~ Claim 1, which further comprises bonding a polyoxyalkylpolyol group to the protein.

Claim 10 (Original): The method according to Claim 9, wherein the protein contains a cysteine residue corresponding to a cysteine residue of the amino acid number 81 in the amino acid sequence of SEQ ID NO: 1, and the polyoxyalkylpolyol group is bonded to said cysteine residue.

Claim 11 (Currently Amended): The method according to Claim 9 ~~or 10~~, wherein the polyoxyalkylpolyol group is a polyethylene glycol group.

Claims 12. – 20. (Canceled).

Claim 21 (Currently Amended): A DNA coding for ~~the protein as defined in any one of Claims 12 to 17~~ a protein comprising an amino acid sequence with a homology of not less than 30% to the amino acid sequence of SEQ ID NO: 1 and forms a secondary or tertiary structure composed of a first β strand (β1), a first α helix (αl), a second α helix (α2), a second β strand (β2), a loop, a third β strand (β3), a fourth β strand (β4) and a fifth β strand (β5) in this order from the amino terminus, and wherein at least one amino acid residue in a region from α2 to β2, a region from β3 to β4, or in the regions from α2 to β2 and from β3 to β4 is replaced so that electric charge of the amino acid residue is substituted towards positive direction as compared to the unsubstituted amino acid, said protein being the following (a) or (b):

(a) a protein, in which the region from α2 to β2 has the sequence of the amino acid residues 47 to 72 in the amino acid sequence of SEQ ID NO: 1 and the region from β3 to β4 has the sequence of the amino acid residues 94 to 111 in the amino acid sequence of SEQ ID NO: 1;

(b) the protein according to (a), in which substitution, insertion or deletion of one amino acid residue is included in the region from α2 to β2 having the sequence of the amino acid residues 47 to 72 in the amino acid sequence of SEQ ID NO: 1, or the region from β3 to β4 having the sequence of the amino acid residues 94 to 111 in the amino acid sequence of SEQ ID NO: 1; and

wherein said protein has antithrombotic activity.

Claim 22 (Currently Amended): A method for producing ~~the~~ a protein having antithrombotic activity ~~as defined in any one of Claims 12 to 17~~, which comprises ~~the steps of~~:

culturing a host microorganism transformed with the DNA as ~~defined~~ claimed in Claim 21;

and collecting the protein from a culture.

Claim 23 (Currently Amended): ~~A~~ The method for producing ~~the~~ a protein ~~as defined in any one of Claims 18 to 20, which comprises the steps of culturing a host microorganism transformed with the DNA as defined in Claim 21, collecting a protein encoded by the DNA from a culture and~~ having antithrombotic activity according to Claim 22, further comprising:

bonding a polyoxyalkylpolyol group to the collected protein.

Claim 24 (Canceled):

Claim 25 (New): A DNA coding for a protein comprising an amino acid sequence with a homology of not less than 30% to the amino acid sequence of SEQ ID NO: 1 and forms a secondary or tertiary structure composed of a first β strand (β1), a first α helix (αl), a second α helix (α2), a second β strand (β2), a loop, a third β strand (β3), a fourth β strand (β4) and a fifth β strand (β5) in this order from the amino terminus, and wherein at least one amino acid residue in a region from α2 to β2, a region from β3 to β4, or in the regions from α2 to β2 and from β3 to β4 is replaced so that electric charge of the amino acid residue is substituted towards positive direction as compared to the unsubstituted amino acid, said protein being the following (a) or (b):

(a) a protein, in which the region from α2 to β2 has the sequence of the amino acid residues 47 to 72 in the amino acid sequence of SEQ ID NO: 1 and the region from β3 to β4

has the sequence of the amino acid residues 94 to 111 in the amino acid sequence of SEQ ID NO: 1;

(b) the protein according to (a), in which substitution, insertion or deletion of one amino acid residue is included in the region from α2 to β2 having the sequence of the amino acid residues 47 to 72 in the amino acid sequence of SEQ ID NO: 1, or the region from β3 to β4 having the sequence of the amino acid residues 94 to 111 in the amino acid sequence of SEQ ID NO: 1; and

wherein said protein has antithrombotic activity,

and wherein said protein comprises an amino acid sequence of the following (A) or (B):

(A) the amino acid sequence of the amino acid residues 47 to 111 in the amino acid sequence of SEQ ID NO: 1;

(B) the amino acid sequence according to (A), in which the cysteine residue of the amino acid residue 81 in the amino acid sequence of SEQ ID NO: 1 is replaced with an alanine residue.

Claim 26 (New): A method for producing a protein having antithrombotic activity, which comprises:

culturing a host microorganism transformed with the DNA as claimed in Claim 25;

and collecting the protein from a culture.

Claim 27 (New): A DNA coding for a protein comprising an amino acid sequence with a homology of not less than 30% to the amino acid sequence of SEQ ID NO: 1 and forms a secondary or tertiary structure composed of a first β strand (β1), a first α helix (αl), a second α helix (α2), a second β strand (β2), a loop, a third β strand (β3), a fourth β strand (β4) and a fifth β strand (β5) in this order from the amino terminus, and wherein at least one amino

acid residue in a region from α2 to β2, a region from β3 to β4, or in the regions from α2 to β2 and from β3 to β4 is replaced so that electric charge of the amino acid residue is substituted towards positive direction as compared to the unsubstituted amino acid, said protein being the following (a) or (b):

(a) a protein, in which the region from α2 to β2 has the sequence of the amino acid residues 47 to 72 in the amino acid sequence of SEQ ID NO: 1 and the region from β3 to β4 has the sequence of the amino acid residues 94 to 111 in the amino acid sequence of SEQ ID NO: 1;

(b) the protein according to (a), in which substitution, insertion or deletion of one amino acid residue is included in the region from α2 to β2 having the sequence of the amino acid residues 47 to 72 in the amino acid sequence of SEQ ID NO: 1, or the region from β3 to β4 having the sequence of the amino acid residues 94 to 111 in the amino acid sequence of SEQ ID NO: 1; and

wherein said protein has antithrombotic activity,

and wherein said protein has the amino acid sequence in which a region containing the loop structure existing between β2 and β3 is deleted in such a manner that the secondary or tertiary structures of β2 and β3 are maintained, or the region is replaced with one or more amino acid residue(s) in a number required to maintain the secondary or tertiary structures of β2 and β3, said amino acid residue(s) being selected from the group consisting of a glycine residue, an alanine residue, a serine residue and a cysteine residue.

Claim 28 (New): A method for producing a protein having antithrombotic activity, which comprises:

culturing a host microorganism transformed with the DNA as claimed in Claim 27;

and collecting the protein from a culture.

Claim 29 (New): The DNA according to Claim 27, wherein the region containing the loop structure existing between β2 and β3 in said protein is replaced with an amino acid sequence composed of four glycine residues.

Claim 30 (New): A method for producing a protein having antithrombotic activity, which comprises:

culturing a host microorganism transformed with the DNA as claimed in Claim 27; and collecting the protein from a culture.

Claim 31 (New): A DNA coding for a protein comprising an amino acid sequence with a homology of not less than 30% to the amino acid sequence of SEQ ID NO: 1 and forms a secondary or tertiary structure composed of a first β strand (β1), a first α helix (αl), a second α helix (α2), a second β strand (β2), a loop, a third β strand (β3), a fourth β strand (β4) and a fifth β strand (β5) in this order from the amino terminus, and wherein at least one amino acid residue in a region from α2 to β2, a region from β3 to β4, or in the regions from α2 to β2 and from β3 to β4 is replaced so that electric charge of the amino acid residue is substituted towards positive direction as compared to the unsubstituted amino acid, said protein being the following (a) or (b):

(a) a protein, in which the region from α2 to β2 has the sequence of the amino acid residues 47 to 72 in the amino acid sequence of SEQ ID NO: 1 and the region from β3 to β4 has the sequence of the amino acid residues 94 to 111 in the amino acid sequence of SEQ ID NO: 1;

(b) the protein according to (a), in which substitution, insertion or deletion of one ~~or~~ amino acid residue is included in the region from α2 to β2 having the sequence of the amino acid residues 47 to 72 in the amino acid sequence of SEQ ID NO: 1, the region from β3 to β4

having the sequence of the amino acid residues 94 to 111 in the amino acid sequence of SEQ ID NO: 1 and

wherein said protein has antithrombotic activity,

and wherein at least one acidic amino acid residue of which α carbon atom exists within 10 Å from the α carbon atom of the arginine residue of the amino acid number 103 in the amino acid sequence of SEQ ID N0: 1 is replaced with a neutral amino acid residue.

Claim 32 (New): A method for producing a protein having antithrombotic activity, which comprises:

culturing a host microorganism transformed with the DNA as claimed in Claim 31;

and collecting the protein from a culture.

Claim 33 (New): The DNA according to Claim 31, wherein in said protein-the acidic amino acid residue to be replaced is composed of at least one residue selected from the aspartic acid residue of the amino acid residue 54, the aspartic acid of the amino acid residue 101 and the glutamic acid residue of the amino acid residue 106 in the amino acid sequence of SEQ ID NO: 1.

Claim 34 (New): A method for producing a protein having antithrombotic activity, which comprises:

culturing a host microorganism transformed with the DNA as claimed in Claim 33;

and collecting the protein from a culture.